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Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 18 (2007) 2300–2304

Solvent-free asymmetric direct aldol reactions organocatalysed by recoverable (S_a)-binam-L-prolinamide

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Received 21 August 2007; accepted 14 September 2007
Available online 10 October 2007

Dedicated to Professor Koichiro Oshima on the occasion of his 60th birthday

Abstract—The combination of (S_a)-binam-L-Pro (5 mol %) and benzoic acid (10 mol %) was used as catalysts in the direct aldol reaction between different aliphatic ketones and 4-nitrobenzaldehyde under solvent-free reaction conditions. Three different procedures are assayed: magnetic stirring (method A), magnetic stirring after previous dissolution in THF and evaporation (method B), and ball mill technique (method C), methods A and B being the simplest. These reaction conditions allowed us to reduce the amount of required ketone to 2 equiv to give the aldol product in similar reaction times and regio-, diastero-, and enantioselectivities than in organic or aqueous solvents.

1. Introduction

The development of sustainable methods for the synthesis of complex molecules is nowadays a main goal in synthetic chemistry[1] and the application of solvent-free reaction conditions[2] meets the established principles for Green Chemistry.[3] On the other hand, the use of small organic molecules as chiral organocatalysts[4] has several advantages concerning handling, cost, and safety issues. Pursuing the sustainability of chemical processes for the synthesis of chiral molecules, the marriage between asymmetric organocatalytic methods and the use of solvent-free environmentally friendly reaction conditions is highly desirable.[5]

The aldol reaction[6] is one of the more inexpensive ways to construct a C–C bond and is extensively applied in industry either in bulk or in fine chemical manufacture and pharmaceutical target production; therefore, the application of 'green conditions' is of great interest.[7] Concomitant with the construction of a C–C bond, a molecule bearing one or more stereogenic centers is created.[8] The use of simple L-proline and other chiral organocatalysts allows the direct aldol reaction using a highly atom-economic process.[9] This is an equilibrium process, which generally requires a large excess of one of the reactants, normally the ketone, to generate the aldol products in good yields. Besides this drawback, some other aspects, such as the long reaction times or the high catalyst loadings need to be improved in the asymmetric organocatalysed direct aldol reaction. Several reaction conditions have been developed in order to achieve higher efficiencies, and only recently the use of solvent-free conditions has been reported.[5b,d,e] Thus, (*S*)-proline (10 mol %) has been used as an organocatalyst for the aldol condensation of symmetrical alkyl ketones and aldehydes using a ball-milling technique, affording the expected aldol in high yields (53–99%) mainly as *anti*-isomers (dr up to 93:7) and with good enantioselectivities (ee's from 56% to 99%) in relatively short reaction times (5–36 h) using only 2 equiv of ketone.[5b,e] The use of conventional magnetic stirring in the same solvent-free reactions gave similar results but longer reaction times were required (1–4 d). These conditions have also been applied to the aldehyde–aldehyde aldol reaction, giving mainly the *anti*-aldol products after 1–4 d with good yields, diastereo- and enantioselectivities (up to 96% ee).[5d,e]

2. Results and discussion

Recently, we and others have studied the use of several binam-prolinamides as catalysts in the aldol reaction under different reaction conditions using alkyl[10] and α-functionalized[11] ketones as a source of nucleophiles, with catalyst

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doi:10.1016/j.tetasy.2007.09.020

(S_a)-binam-L-Pro **1a** (Fig. 1) providing the best results.[10a] We found that the addition of benzoic acid as a cocatalyst led to a great acceleration of the reaction, thus allowing the use of less reactive ketones, such as butanone[10c] and α-functionalized ketones even 'on' water,[10f,11] to give the corresponding aldol products with a high level of selectivity. In addition, catalyst **1a** can also be recovered by simple extractive work-up after reaction completion.[11a,c] Herein, we report the highly regio-, diastereo-, and enantioselective direct intermolecular aldol reaction under solvent-free conditions, cocatalyzed by binam-L-prolinamides **1a** and **1b** and benzoic acid in short reaction times and using only 2 equiv of several cyclic and acyclic aliphatic ketones.

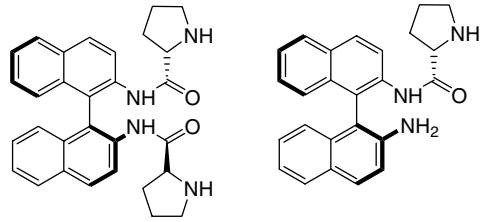


Figure 1. Binam-L-proline derived catalysts.

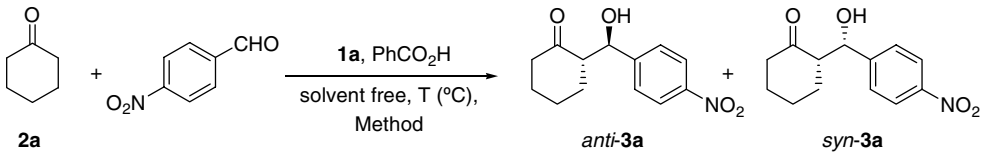
Catalysts **1a** and **1b** were synthesized in 97% and 58% yield, respectively, by coupling commercially available (*S*)-1,1′-binaphthyl-2,2′-diamine [(S_a)-binam] with in situ generated Fmoc-L-Pro chloride (2.1 and 1 equiv, respectively), followed by deprotection with piperidine.

The model reaction of 4-nitrobenzaldehyde and 2 equiv of cyclohexanone at 25 °C using 10 mol % of **1a** and 20 mol % of benzoic acid as a catalytic combination was carried out using three different methods: conventional magnetic stirring (method A); conventional magnetic stirring with a pre-formed solution in THF and immediate evaporation of the solvent, which should induce an enhancement of molecule-to-molecule contacts between the reactants and therefore an acceleration of the reaction rate (method B),[12] and ball-milling conditions (method C). The aldol products **3a** were obtained after only 1–1.5 h with quantitative conversions and similar results concerning diastereo- and enantioselectivities using the three methods (Table 1, entries 1–3). In all cases, the *anti*-isomer was obtained with moderate diastereoselectivity. The study of other reaction parameters was done by using conventional magnetic stirring due to simplicity reasons.

When the temperature was lowered to 0 °C, using 10 mol % of **1a** and 20 mol % of benzoic acid and using methods A and B, an increase in the reaction time but also in the diastereo- and enantioselectivity, up to 93% ee for *anti*-**3a**, was observed, with slightly better results being obtained using method B (Table 1, entries 4 and 5). Reducing the amount of catalyst **1a** and benzoic acid to 5 mol % and 10 mol %, respectively, led to an increase in the reaction time, with a slight increase on the diasteroselectivities achieved (Table 1, entries 6 and 7). The use of catalyst **1b** (5 mol %) was less efficient than catalyst **1a** affording product **3a** in 8 h (Table 1, compare entries 6 and 8).

When L-proline (10 mol %) was used as a catalyst under method B conditions, low conversion was observed even after 24 h reaction time, although product **3a** was formed with excellent diastereo- and enantioselectivity (Table 1, entry 9). In order to increase the conversion, benzoic acid (10 mol %) was added to the reaction mixture, forming

Table 1. Optimization of conditions for the reaction of 4-nitrobenzaldehyde with cyclohexanone under solvent-free conditions[a]



2a *anti*-**3a** *syn*-**3a**

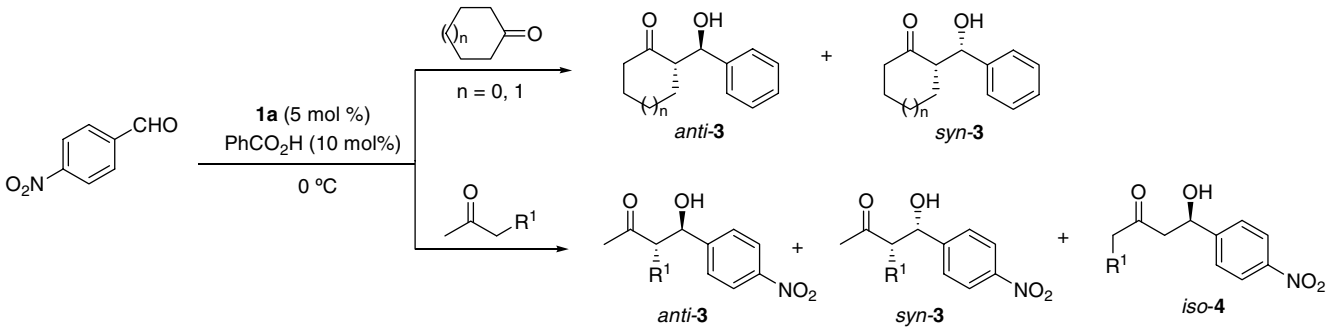
Entry	Method[b]	Catalyst (mol %)	Benzoic acid (mol %)	*T* (°C)	*t* (h)	Conversion[c] (%)	*anti*/*syn*[d]	ee[e] (%)
1	A	**1a** (10)	20	25	1.0	99	67:33	88
2	B	**1a** (10)	20	25	1.5	99	72:28	89
3	C	**1a** (10)	20	25	1.5	100	69:31	88
4	A	**1a** (10)	20	0	1.5	80	83:17	90
5	B	**1a** (10)	20	0	2.0	94	89:11	93
6	A	**1a** (5)	10	0	2.0	99	90:10	86
7	B	**1a** (5)	10	0	4.0	94	93:7	90
8	A	**1b** (5)	10	0	8.0	85	87:13	83
9	B	L-Pro (10)	—	0	24	34	96:4	96
10	B	L-Pro (10)	10	0	24	60	94:6	94

[a] The reaction was carried out using 4-nitrobenzaldehyde (0.25 mmol) and cyclohexanone (2 equiv).
[b] Method A: conventional magnetic stirring. Method B: 4-nitrobenzaldehyde, catalyst and benzoic acid were dissolved in dry THF (0.5 mL) and the solvent was evaporated prior to the addition of cyclohexanone. Method C: the grinding bowl containing the reaction mixture was rotated in a ball mill at rotation speed of 300 rpm.
[c] Conversion based on the unreacted aldehyde.
[d] Determined by ^{1}H NMR of the crude product.
[e] Determined by chiral-phase HPLC analysis for the *anti*-**3a** isomer.

aldol **3a** with higher conversion (60%) after the same reaction time (Table 1, entry 10). It can be concluded that the best compromise between reaction rate, diastereo- and enantioselectivity was achieved by using 5 mol % of **1a** in the presence of 10 mol % of benzoic acid at 0 °C either under method A or B conditions, with longer reaction times required when using method B, but with slightly higher diastereo- and enantioselectivity (Table 1, entries 6 and 7).

Once the best reaction conditions were found, these were applied to study the scope of the solvent-free process (Scheme 1 and Table 2). Thus, cyclohexanone exclusively gave the *anti*-**3a** product in high enantioselectivity using methods A or B (Table 2, entries 1 and 2), the use of cyclopentanone afforded a nearly 1:2 mixture of *anti*/*syn*-**3b** isomers with higher ee for the *anti*-isomer (Table 2, entries 3 and 4). Generally, the results achieved using method A are comparable to those obtained using method B but with longer reaction times needed when using the last method.

Several alkyl ketones such as acetone and butanone and α-functionalized ketones as nucleophiles were then employed in the reaction with 4-nitrobenzaldehyde. When acetone **2c** was used as a donor, the aldol product **3c** was obtained in

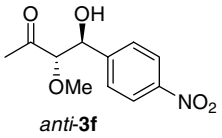
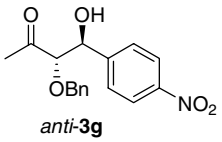
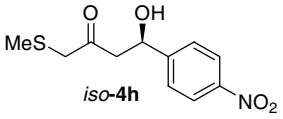


Scheme 1. Reaction of 4-nitrobenzaldehyde with different ketones under solvent-free conditions.

Table 2. Reaction of 4-nitrobenzaldehyde with different ketones under solvent-free conditions[a]

Entry	Method	Major product	*t* (h)	Yield[b] (%)	Isomer ratio[c]		ee[d] (%)
					Regioselectivity (**3**/**4**)	dr (*anti*/*syn*)	
1	A	*anti*-**3a**	2	99 (80)	—	90:10	86[e]
2	B		4	94 (85)	—	97:3	90[e]
3	A	*anti*/*syn*-**3b**	3	92 (64)	—	30:70	80:63
4	B		7	97 (86)	—	28:72	80:46
5	A	**3c**	3	86	—	—	74
6	B		8	88	—	—	74
7	A	*anti*-**3d**	24	96 (90)[f]	63:37	>99:1	97 (91)[g]
8	B		40	97	55:45	>99:1	90 (99)[g]
9	A	*anti*-**3e**	4	76	>99:1	75:25	16[e]
10	B		21	92	49:1	64:36	20[e]

Table 2 (*continued*)

Entry	Method	Major product	*t* (h)	Yield[b] (%)	Isomer ratio[c]		ee[d] (%)
					Regioselectivity (**3/4**)	dr (*anti*/*syn*)	
11	A	 *anti*-**3f**	4	90 (78)	94:6	83:17	60[e]
12	B		21	91 (84)	91:9	83:17	80[e]
13[h]	A	 *anti*-**3g**	78	92 (78)	97:3	86:14	84[e]
14[h]	B		89	96	88:12	83:17	86[e]
15	A	 *iso*-**4h**	48	83 (74)	16:84	50:50	86[i]
16	B		168	70	27:73	59:41	90[i]

[a] General reaction conditions: 4-nitrobenzaldehyde (0.25 mmol), ketone (2 equiv) (S_a)-binam-L-Pro **1a** (5 mol %) and benzoic acid (10 mol %) at 0 °C, otherwise stated. After completion of the reaction performed under method A or B (see Table 1), 1 M HCl (10 mL) and ethyl acetate (20 mL) were added. The organic phase was separated, dried and evaporated to afford the crude products, which were purified by flash chromatography.
[b] Yield of the isolated crude product. In parenthesis, yield of the pure product after column chromatography.
[c] Determined by ^{1}H NMR of the crude product.
[d] Determined by chiral-phase HPLC analysis.
[e] For the *anti*-isomer.
[f] Overall yield for both isolated isomers by column chromatography.
[g] In parenthesis, enantiomeric excess for the *iso*-**4d** isomer.
[h] The reaction was carried out at −20 °C.
[i] For the *iso*-isomer.

only 3 h using method A, with 86% yield and 74% ee (Table 2, entry 5), better results than those reported by using the ball-milling technique and L-Pro (19 h reaction time, 73% yield, 56% ee).[5b,e] Similar results were obtained under method B conditions but in a longer reaction time (Table 2, entry 6).

In the case of 2-butanone, a mixture of *anti*-**3d** and *iso*-**4d** regioisomers with excellent enantioselectivities (97% and 91% ee, respectively) were obtained in only 1 d reaction time using method A (Table 2, entry 7). Although, the reaction under method B conditions led to a nearly 1:1 mixture of the *anti*-**3d** and *iso*-**4d** with a longer reaction time, the last compound was obtained as only one enantiomer (Table 2, entry 8).

When α-functionalized ketones were used as donors, the results were dependant on the functionality. When α-oxygenated ketones were used as donors, good yields and regioselectivities were achieved in all cases. However, whereas α-hydroxyacetone **2e** gave very poor enantioselectivities (Table 2, entries 9 and 10), α-methoxyacetone **2f** and α-benzyloxyacetone **2g** both gave mainly the *anti*-aldols **3f** and **3g**, respectively, with higher enantioselectivities (Table 2, entries 11–14). In the case of α-methoxyacetone **2f**, better enantioselectivities were achieved by carrying the reaction under method B conditions (Table 2, entry 12), whereas α-benzyloxyacetone **2g** gave the best regio- and diastereoselectivity under method A conditions (Table 1, entry 13). It can be concluded that α-methoxyacetone reacted faster than α-benzyloxyacetone, although the latter gave better ee.

Finally, α-(methylsulfanyl)acetone **2h** was used as a nucleophile, affording mainly the *iso*-**4h** product with a regioselectivity of 1:5 and 86% ee (Table 2, entry 15). The use of method B to carry out the reaction led to a long reaction time (7 d) without improving the obtained results.

These results are rather similar to those previously described in aqueous media.[11b] L-Pro (10 mol %) was also employed as a catalyst under method B reaction conditions for ketones **2f** and **2g**, only reaction being observed in the case of α-methoxyacetone **2f**, affording the aldol product **3f** with 3% conversion after 2 d, with 80:20 de and 94% ee for the *anti*-**3f** diastereomer.

3. Conclusion

It can be concluded that catalyst (S_a)-binam-L-Pro **1a** combined with benzoic acid is a better catalyst system than L-Pro to be used in the direct aldol reaction of a wide scope with ketones under solvent-free conditions using simple conventional magnetic stirring. This procedure allowed us to reduce the amount of required ketone to 2 equiv, forming the aldol product in similar reaction times comparing to using solvents.[10,11] The same observation was found with respect to the regio- diastero-, and enantioselectivity. Generally, *anti*-isomers were obtained with

enantioselectivities (from 16% to 97%) highly dependent on the ketone. These results are better than those previously reported using ball-milling techniques and L-proline as a catalyst,[5b,e] with the additional advantage that a simpler conventional magnetic stirring is used.

Acknowledgments

This work was financially supported by the Dirección General de Investigación of the Ministerio de Educación y Ciencia of Spain (Grant CTQ2004-00808/BQU and Consolider Ingenio 2010 CSD2007-00006), the Generalitat Valenciana (Grant CTIOIB/2002/320, GRUPOS03/134 and GV05/157) and the University of Alicante (GRJ06-05).

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